# AMERICAN CHEMISTRY COUNCIL

## Biocides Panel
## Chromated Copper Arsenate Work Group

## Comments to EPA SAB Arsenic Review Panel (September 12–13, 2005) Regarding Inorganic Arsenic Carcinogenicity

EPA has requested comments and advice from the Science Advisory Board (SAB) regarding EPA's recent hazard characterization for organic arsenic herbicides and on their revised hazard and dose-response assessment/characterization of inorganic arsenic. The issues and questions for the SAB to consider are outlined in EPA's *Charge to EPA Science Advisory Board Arsenic Review Panel*. EPA has also provided two other documents for SAB review that outline EPA's approach for revising the inorganic arsenic slope factor: *Issue Paper: Inorganic Arsenic Cancer Slope Factor* and *Toxicological Review of Ingested Inorganic Arsenic*.

The American Chemistry Council Biocides Panel CCA Work Group provides additional comments for EPA and the Science Advisory Board Arsenic Review Panel to consider in evaluating EPA's Charge regarding inorganic arsenic including comments that relate to the broader issue of the best use of the state of the science in revising the inorganic arsenic cancer slope factor. The specific comments present (1) epidemiological evidence from the United States in addition to the recent drinking water studies discussed by the Toxicological Review and by the meta-analysis of Dr. Pamela Mink; (2) implications of the proposed cancer slope factor for background risks in the United States; (3) recent studies on the effect of nutritional deficiency in increasing arsenic toxicity; and (4) evidence supporting elevated water intake rates in the southwest Taiwanese population as compared to the United States.

## Additional Epidemiological Evidence from the United States

The EPA draft Toxicological Review and draft Issue Paper discuss several United States epidemiological studies that were published since the NRC (2001) review. These studies and a

few other recent epidemiological studies are also included in a meta-analysis of studies of low-level exposure to arsenic in drinking water and risk of bladder cancer conducted by Dr. Pamela Mink. It is ACC's understanding that the results of this meta-analysis will be submitted to the SAB separately.

In addition to the studies included in the meta-analysis, a number of other studies also examined the association between environmental arsenic exposure and cancer. These studies did not meet the criteria for inclusion in the above meta-analysis but nevertheless provide additional qualitative epidemiological evidence regarding low-level exposures in the U.S. These studies include evaluations of populations exposed to arsenic in drinking water and of communities exposed to arsenic in air, dust, and soil from living near arsenic-emitting industrial facilities. A few other studies from smelter sites in Canada and Sweden were also reviewed. Evidence from these additional studies (summarized in Attachment 1) is generally negative for associations with arsenical cancers and consistent with the meta-analysis findings.

Additional drinking water studies that have examined cancer include populations from Oregon (basal and squamous cell carcinoma; Morton et al. 1976), Nevada (childhood leukemia; Moore et al. 2002), New Hampshire (basal and squamous cell carcinoma; Karagas et al. 2001), and Wisconsin (lung, bladder, and non-melanoma skin cancers; Knobeloch 2002), and two studies involving multiple states (34 cancers; Berg and Burbank 1972; malignant neoplasms, lung cancer; Engel and Smith 1994). With the exception of Knobeloch (2002), these studies were negative for cancer risks potentially associated with arsenic. Knobeloch (2002) reported increased risks for non-melonoma skin cancer in the highest arsenic water exposure group who were 65 years and older and were smokers. The highest water exposure group, however, included a wide range in well water concentrations from 5 $\mu$g/L to more than 3,000 $\mu$g/L. Thus, without specific information on exposures of cases within this group, the relevance of these results for low-level exposures in the general population is unclear.

Most of the studies of communities near smelters (or in one case an arsenical pesticide plant) evaluated associations with lung cancer. These studies have been generally negative for lung or other cancers examined related to arsenic, with the exception of three studies that found associations with lung cancer in men (Attachment 1). Populations near arsenic emitting

industrial facilities would be expected to be at higher risk for lung cancer. In addition to the association between oral arsenic exposure and lung cancer (e.g., Chen et al. 2004), increased risk of lung cancer has been reported following very high dose inhalation exposures to arsenic (e.g., time-weighted average air levels from 213 to 1,487 $\mu g/m^3$ for low to high exposure groups) in historical smelter or chemical workers after years of exposure (ATSDR 2000). Airborne emissions from these smelters also resulted in greatly elevated soil arsenic concentrations (up to 1,000 ppm and above in some cases). Thus, communities residing near smelters would be expected to be exposed by oral exposure to dust deposited on surfaces and soil and via inhalation exposure, both routes that are associated with lung cancer. These industrial facilities typically also had a long history of operation pre-dating air pollution controls and would also have emitted other potential lung carcinogens or co-carcinogenic substances (e.g., combustion by-products, polycyclic aromatic hydrocarbons, other carcinogenic metals, sulfur dioxide).

The community near a former copper smelter (1912 to 1986) in Tacoma, Washington, is one of the best-studied of such communities. Community residents were studied in numerous health monitoring and epidemiological studies conducted by local and state health departments and the University of Washington. Two epidemiological studies (Frost et al. 1987; WSDH and ATSDR 1994) examined lung cancer mortality and a third follow-up study (Tollestrup et al. 2003) examined a number of types of cancer in people who lived near the Tacoma smelter when it was operating, extending back to the early 1900s. These studies did not report an increase in lung or other cancers related to arsenic exposure in this population.

Historical exposures to arsenic near the Tacoma smelter would have been considerably higher than records of arsenic levels in the community taken after the advent of modern air pollution control regulations and devices. Even in the late 1970s and early 1980s with air pollution controls, air levels in the nearby community were on average 0.8 $\mu g/m^3$ with an occasional elevation to 10 $\mu g/m^3$ (Frost et al. 1987; Milham 1988). Elevated exposures were also apparent in the residential population. Speciated urinary arsenic levels (sum of inorganic arsenic, monomethylarsonic acid, dimethylarsinic acid resulting from absorption and metabolism of inorganic arsenic) in children during the time of smelter shutdown and shortly afterward in the early 1980s averaged 52 $\mu g/L$ (Polissar et al. 1987) compared to about 7 $\mu g/L$ for the remote

population of the Anaconda smelter site measured long after that smelter had shut down (Hwang et al. 1997).

In addition to health studies in Washington, studies have been conducted at other communities near smelting and mining sites, the majority of which have focused on lung cancer (Lyon et al. 1977; Greaves et al. 1981; Rom et al. 1982; CDPHE 1995; Marsh et al. 1997, 1998), although Wong et al. (1992) examined skin cancer. These studies likewise do not indicate an increase in health risks associated with arsenic exposure.

Studies reporting an increased risk involved two smelters in Sweden (Pershagen et al. 1985), Canada (Cordier et al. 1983), and an arsenical pesticide plant in Baltimore, Maryland (Matanoski et al. 1981). These studies found increased risks of lung cancers only in men (Perhagen et al. 1985 evaluated only men).

Thus, consistent with the results of the meta-analysis, these additional studies largely in U.S. populations likewise indicate little evidence of increased cancer risk at low-level arsenic exposures.

## Implications for Background Arsenic Risks

As a naturally occurring element, arsenic is ubiquitous in soil, water, and food (ATSDR 2000). If arsenic is assumed to have no lower threshold for cancer risk according to EPA assumptions, any dose of arsenic is associated with some cancer risk. Because risk assessments currently predict risks greater than one in a million even for background exposures to arsenic at the current slope factor, the typical definition of *de minimis* risk is less useful for risk communication. Risk communication for arsenic will become even more difficult if EPA increases their arsenic cancer potency factor according to the recommendations in the cancer work group issue paper based largely on the reanalysis by NRC (2001). As described below, risk estimates associated with typically occurring background exposures will be much higher than the 1 in 10,000 upper end of the ‘acceptable’ risk range identified by EPA.

As an illustration of background diet and water risk, intake of inorganic arsenic in food and water in the U.S. population were stochastically modeled based on Yost et al. (2004) including inorganic arsenic in different foods (Schoof et al. 1999), regional water concentrations reported by U.S. EPA (2001), and U.S. Department of Agriculture Continuing Survey of Food Intake by Individuals (USDA CSFII; years 1994–1996 for the total population). The effect of truncating the arsenic water concentration distribution was evaluated assuming the complete implementation of the revised drinking water standard of 10 $\mu$g/L. Arsenic water concentration levels above 10 $\mu$g/L were assigned lower arsenic water concentrations in proportion to their occurrence in the dataset below 10 $\mu$g/L. Two estimated intakes were thus calculated for diet and water combined, using the two different water concentration distributions. The lower estimate reflects truncation of the water data at 10 $\mu$g/L, the revised standard for arsenic in water. The results of this analysis indicate mean diet and water concentration intakes of 5.4 to 6.1 $\mu$g/day for the U.S. population. To calculate upper end estimates for certain segments of the population, intakes were also calculated at the 90th percentile: 10.5 $\mu$g/day and 11.1 $\mu$g/day. Intakes above the 90th percentile are typically assumed by the FDA to represent lifetime exposure to substances in food for the upper end of the population who are more exposed than the average consumer (U.S. FDA 1995). Lifetime risks were calculated using an assumed lifetime average body weight of 70 kg, according to standard EPA assumptions. Risk estimates rounded off to similar numbers for estimates based on the U.S. EPA (2001) water data and based on the truncated water data.

As a comparison, risks associated with various arsenic concentrations in soil were calculated according to standard EPA assumptions for Superfund risk assessments (U.S. EPA 1991) with a typical default bioavailability of 80 percent gastrointestinal absorption for arsenic in soil. The risk associated with consuming water at the new drinking water standard of 10 $\mu$g/L was also calculated based on standard EPA Office of Water assumptions for lifetime exposure of 2 L/day and 70 kg body weight.

Risks associated with mean dietary and water arsenic intake and consumption of water at the new arsenic drinking water standard using the current slope factor of 1.5 per mg/kg/day are at or slightly above EPA's upper limit for acceptable risk of 1 in 10,000 ($1\times10^{-4}$). Risks for arsenic

in soil approach this level at 50 ppm. With the revised slope factor of 5.7 per mg/kg-day developed by EPA's draft Toxicological Review document, dietary, water, and background soil risks are all well above the 1 in 10,000 acceptable risk level (Table 1; risk calculations in Attachment 2) and would signal the need for regulatory action.

**Table 1. Risk estimates for background diet and water intakes, water at 10 μg/L and different soil concentrations using the current and proposed cancer slope factors**

| | Cancer Risk for | | | | | |
|---|---|---|---|---|---|---|
| Slope Factor $(mg/kg/day)^{-1}$ | Mean Diet and Water Intake | 90th Percentile Diet and Water Intake | Water at 10 μg/L | Soil at 20 ppm | Soil at 50 ppm | Soil at 100 ppm |
| 1.5 | $1\times10^{-4}$ | $2\times10^{-4}$ | $4\times10^{-4}$ | $4\times10^{-5}$ | $1\times10^{-4}$ | $2\times10^{-4}$ |
| 5.7 | $5\times10^{-4}$ | $9\times10^{-4}$ | $2\times10^{-3}$ | $2\times10^{-4}$ | $4\times10^{-4}$ | $8\times10^{-4}$ |

Although this perspective might be considered more risk management than science, the results indicate that overly conservative policy in the face of any uncertainty (even when evidence indicates that actuality is more likely in the other direction) can have important consequences for public perception of risk and setting regulatory and public health policies and priorities for addressing health risks in the U.S.

## Nutritional Deficiency

Nutritional deficiency in the southwest Taiwanese population is another factor that affects the relevance of this population for the United States. NRC (2001) dismissed the importance of the nutritionally impoverished conditions for the southwest Taiwanese population studied by Morales et al. (2000), stating that that nutritional deficiency could not account for the observed cancers. The question that should be considered, however, is the effect of nutritional deficiencies on the dose-response relationship. Specifically, although elevated arsenic exposure is known to be associated with increased cancer risk, nutritional deficiencies, particularly in those exposed at higher doses (i.e., doses at which arsenical health effects and increased risk of

cancer have been reported), might have increased the susceptibility of the southwest Taiwanese population to the toxic effects of arsenic. Such a factor may increase the apparent dose-response relationship for this population over a nutritionally sufficient population.

Since NRC (2001), several additional studies have been published on the importance of nutritional deficiencies in various substances on potentiating arsenic toxicity and carcinogenicity (Chen et al. 2001; Milton et al. 2004; Mitra et al. 2004; Spallholz et al. 2004; Schoen et al. 2004) by interfering with arsenic methylation, defenses against oxidative stress, or with DNA repair.

Various nutrients such as B-vitamins, methionine, and folate may play important roles in enzymatic methylation of arsenic. Individuals in Taiwan with skin cancer had a lower methylation capacity (less DMA formation) compared to healthy controls (Chen et al. 2001).

Chen et al. (2001) summarize studies reporting that undernourishment in southwest Taiwan, as indicated by long-term ingestion of yams and low serum levels of carotene, increased the risk of skin cancer and other diseases related to arsenic exposure. Chen et al. (2001) also note that impoverished diets in this region were dominated by yams with few fresh fruits and vegetables and a little fish as the only protein source. Overall, the diet was high in carbohydrates, low in protein, and extremely low in fat including essential unsaturated fatty acids. Two amino acids that appear to be deficient are methionine and tryptophan, which may play key roles in arsenic biotransformation. Vitamin intake (e.g., beta carotene) was also marginal. A number of studies in Taiwan have associated these nutritional factors along with lower socioeconomic status with an increased risk of arsenic-related diseases.

Mitra et al. (2004) conducted a case-control study of the effect of nutrition on susceptibility to arsenical health effects in a population in West Bengal, India, exposed to arsenic levels in drinking water up to 500 $\mu$g/L. Low intake of animal protein, calcium, and fiber were significantly related to increased risk of arsenical skin lesions. Folate was also close to significance as a risk factor.

Milton et al. (2004) examined the nutritional status among chronically arsenic-exposed and unexposed populations in Bangladesh. Individuals (138) with arsenicosis from arsenic endemic villages (mean well water arsenic of 641 $\mu$g/L) were matched by age and sex with 144 unexposed subjects randomly selected from villages with low arsenic in well water (mean of 13.5 $\mu$g/L). A crude prevalence ratio of 1.92 (95% CI = 1.33–2.78) was found for poor nutritional status among the arsenicosis cases compared to the control population. This finding indicates that poor nutritional status may increase risk of arsenic toxicity or that arsenic toxicity may result in poor nutritional status. A better control population to examine the effects of poor nutrition on risk of arsenical health effects would have been to match the cases with similarly exposed subjects without arsenicosis.

Spallholtz et al. (2004) reviewed evidence from various studies both *in vitro* and *in vivo* in humans and animals that indicates that selenium counteracts arsenic toxicity and selenium deficiencies can increase arsenic toxicity. For example, glutathionine peroxidases and other antioxidant proteins containing selenium help counteract oxidative stress produced by arsenic. Oxidative stress is one of the main mechanisms by which arsenic is thought to produce toxicity and carcinogenicity. Deficiencies in selenium as well as other micronutrients (e.g., zinc, vitamin E) can thus lead to insufficient antioxidant activity and greater risk of arsenic-related health effects. The complex of arsenic, selenium, and glutathione appears to be a route of excretion for excess arsenic ingestion through hepato-biliary elimination and fecal excretion. Miyazaki et al. (2005) likewise report that selenium-deficient pregnant mice show enhanced accumulation of arsenic in maternal liver and fetal brain. Impaired biliary excretion of arsenic may therefore result in increased liver accumulation and extra urinary excretion of arsenic and thereby increased bladder cancer risk.

Spallholtz et al. (2004) also note that very low selenium in soil and likely in the food chain in Bangladesh may have enhanced the toxicity of arsenic to populations exposed to elevated arsenic in well water. Clinical trials of patients with arsenical disease in Inner Mongolia, China, showed reduction in blood and hair arsenic levels and significant improvement of arsenical skin lesions with selenium supplementation as compared to controls (Yang et al. 2002).

Thus, additional studies since NRC (2001) continue to underscore the impact of deficiencies in selenium and other antioxidant micronutrients in enhancing arsenic toxicity. Consequently, nutritional deficiency is an important factor to consider in evaluating the relevance of extrapolations of the dose-response assessment of the southwest Taiwanese data for U.S. populations.

## Water Intake Rates in Taiwan

NRC (2001) and EPA (2005) have concluded that water intake rate by the southwest Taiwanese population can have a large effect on the calculated arsenic cancer slope factor for the U.S. population. The Taiwanese population was impoverished and thus their fluid intake was likely well water rather than purchased beverages. Water consumption in this population would also be elevated over the U.S. population by the hot, humid, climate, and by employment as laborers.

The EPA 2005 draft Issue Paper summarizes various studies on drinking water intake rates and concludes "the mean adult drinking water consumption rate for Asian populations is between 1 to 4.6 L/day." However, studies that focus on populations in hot conditions indicate means of 3 to 3.7 L/day. The only indication of intakes of 1 L/day is the lower end of the range from an informal interview of people in Taiwan reported in a 1961 paper or the mean for U.S. populations. The studies summarized by the Issue Paper do not include a paper by EPA Office of Water scientists and contractors that was presented at the 2004 Society of Toxicology annual meeting. This paper was also provided as a handout at the meeting (Attachment 3). This paper reports a seasonal average intake of 3.6 L/day for drinking water consumption under the conditions of the population in southwest Taiwan. Thus, the available evidence does not support a mean drinking water consumption rate for this population as low as 1 L/day.

In addition to drinking water, this population consumed a diet of dried yams and rice, which had to be rehydrated and cooked in well water. In developing the reference dose for arsenic available in EPA's Integrated Risk Information System (IRIS) database, EPA estimated the amount of water used in rehydration and cooking to be an additional 1 L/day (http://www.epa.gov/iris/subst/0278.htm). The same assumption was made by U.S. EPA

(2001). In developing the RfD, EPA assumed a total water ingestion rate of 4.5 L/day from direct consumption as well as indirect consumption through the diet. EPA also assumed a 2 $\mu$g/day contribution from arsenic in food, which has subsequently been shown by actual measurements of inorganic arsenic in yams and rice in Taiwan to be 50 $\mu$g/day (Schoof et al. 1998). The IRIS record cites an EPA memorandum by Abernathy et al. (1989). This memorandum documents the water intake and dietary intake assumptions used in the reference dose calculation and is attached (Attachment 4).

Both NRC (2001) and the EPA 2005 draft Issue Paper note that the assumption of an additional 1 L/day of water from dietary use by EPA (2001) is undocumented and neither mentions the EPA IRIS record or Abernathy et al. (1989). However, EPA concluded in their Issue Paper that this amount was justified by the literature. EPA's current slope factor calculations in the draft Toxicological Review, however, do not appear to include this additional water intake and the Charge neglects to ask the SAB about additional water used in rehydrating and cooking food.

Thus, the scientific evidence supports a total water intake by the Taiwanese population used in the slope factor calculation of 4.5 L/day and above.

## Conclusions

Considerable evidence from the United States supports a lower risk of arsenical cancers at low doses than projected based on extrapolations from the data in the southwest Taiwanese population. In addition to recent studies conducted in populations exposed to arsenic in drinking water, other studies of populations exposed to arsenic in drinking water or to arsenic in air, dust, and soil near arsenic emitting industrial facilities overall show little indication of elevated arsenical cancer risk for the general U.S. population.

Nevertheless, background risks associated with inorganic arsenic in the food, water, and soil will exceed acceptable risk levels using the proposed cancer slope factor based on modeling from the southwest Taiwanese data. The accuracy of the risk characterization for arsenic

therefore has important consequences for public perception of risk and setting regulatory and public health priorities for addressing health risks in the United States.

Areas of uncertainty in risk characterization using the Taiwanese data include the impact of nutritional deficiencies of this population on arsenic toxicity and higher water intake on arsenic dose as compared to the United States. Considerable recent evidence reinforces earlier findings that the southwest Taiwanese diet was deficient in several micronutrients that are important for reducing arsenic toxicity and potential carcinogenicity. Likewise, the weight of evidence from evaluations to date is sufficient to conclude that the drinking water intake rate (including water used for rehydrating and cooking food) of the southwest Taiwanese population was likely 4.5 L/day and possibly greater. This evidence should be taken into account in any considerations of the southwest Taiwanese data for estimating cancer risks in the United States. These uncertainties and others indicate that greater weight should be placed on studies from the United States and other nutritionally sufficient populations.

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# Attachment 1

# Additional Epidemiological Studies of Low-Level Arsenic Exposure

## Attachment 1. Additional epidemiological studies of lower-level arsenic exposure

| Reference | Study Location | Study type | Study Population (Exposed) | Sample Size and Number of Observed or Exposed | Range of Arsenic Exposure Levels | Study Findings |
|---|---|---|---|---|---|---|
| **U.S. Water Exposure** | | | | | | |
| Karagas et al. 2001 | New Hampshire | Case control | Newly diagnosed cases (July 1993-June 1995), aged 25-74. Identified by dermatologists and pathology labs. N=603 BCC and 293 SCC (cases interviewed).<br><br>State includes areas with elevated arsenic in well water. | BCC cases N=587<br>SCC cases N=284<br>Controls N=524 | Toenail arsenic concentrations (µg/g)=<br>BCC cases: 0.01-2.03<br>SCC cases: 0.01-2.57<br>Controls: 0.01-0.81 | "Toenail arsenic concentrations were unrelated to risk at levels most commonly encountered in the population we studied." (p. 561)<br><br>"Adjustment for other covariates had no appreciable effect on relative risk estimates." (p. 561) |
| Knobeloch 2002 | Wisconsin (Outagamie and Winnebago counties) | Cross sectional | Respondents to well-water testing program and family water use and health history questionnaire between June 2000 and January 2002.<br><br>2,223 families responded comprising a total of 6,669 individuals including 522 pre-school aged children and 752 adults over the age of 65. | All cancers N=380<br><br>Bladder cancer N=11<br><br>Lung cancer N=13 (12 diagnosed while living in current residence)<br><br>Skin cancer:<br>Melanoma N=25 (19 diagnosed while living in current residence)<br>Non-melanoma N=122 (95 diagnosed while living in current residence) | 0-3,100 µg/L | No significant increases in bladder cancer or lung cancer risk. Increased skin cancer risks for smokers aged 65 and older in the highest well water exposure group ≥ 5 µg/L (OR = 4.79; 95% CI = 1.92-11.96). |
| Berg and Burbank 1972 | 16 river basins nationwide | Ecological | Cancer mortality from each of 34 cancers. 18-year incidence rates were calculated separately for four groups: white men, white women, nonwhite men, and nonwhite women. | Not given | Not given | No correlation between arsenic water concentration measurements and skin cancer, lung cancer, or other cancers associated with arsenic |
| Engel and Smith 1994 | 30 U.S. counties in 11 states | Ecological | Mortality data for whites from NCHS and population data from the U.S. Census Bureau (1968-1984) in the counties with a mean arsenic level of at least 5 µg/L. | Malignant neoplasms:<br>M: 22,971<br>F: 18,849<br>Lung Cancer:<br>M: 7,274<br>F: 2,538 | 5.4-91.5 µg/L;<br>Exposure categories (µg/L):<br>5-10, 10-20, >20 | "Mortality due to malignant neoplasms was also close to expected in the three arsenic categories in both genders." (p. 420)<br><br>"Lung cancer mortality in females was within the expected and was smaller than expected for males in the two higher arsenic categories." (p. 423) |
| Moore et al. 2002 | Nevada | Ecological | All children aged 0-19 living in Nevada 1979-1999. N=327,947 (Pop. was determined by 1990 census data.) Cancer incidence rates obtained from the state cancer registry. | All cancers N = 1,003<br>Leukemia cases:<br>High Exposure: 8 out of 11,370; Medium Exposure 3 out of 8,751; Low Exposure 257 out of 311,173 | 0.0–91.5 µg/L<br>Exposure Category (µg/L):<br>Low: < 10; Medium: 10–25; High: 35–90 | No significant increases associated with arsenic in water for leukemia or all nonleukemia childhood cancers combined. |

## Attachment 1. (cont.)

| Reference | Study Location | Study type | Study Population (Exposed) | Sample Size and Number of Observed or Exposed | Range of Arsenic Exposure Levels | Study Findings |
|---|---|---|---|---|---|---|
| Morton et al. 1976 | Oregon (Lane County) | Ecological | Histopathologically confirmed cases of skin cancer among Lane County residents diagnosed during 1958–1971. | 3,691 cases of nonmelanoma (BCC and SCC) skin cancer among 3,237 individuals | Water arsenic (µg/L)<br>Entire Lane County: 0–2,150<br>Rural: 0–2,150<br>Urban: 0–860 | "Neither type of skin cancer was directly related to arsenic levels." (abstract) Increases in BCC with urban exposure. |
| **Other U.S. Studies** | | | | | | |
| Tollestrup et al. 1995 | Wenatchee, Washington | Cohort | Individuals who lived in the Wenatchee area (where lead arsenate spray was used for a longer time period [more than 25 years] and in larger amounts than in other areas in the U.S.) during the 1938 apple growing season and who had participated in the 1938 Neal study and the 1968 Nelson study.<br>Cohort (N=1,225) divided into three exposure groups: Consumers (no occupational spray exposure), N=292; Intermediates (no spray use in 1938 or infrequent exposure to spray), N=296; and Orchardists (prepared and applied spray during growing season), N=535. | All cancers, M: 84; F: 39<br>Lung cancer: 1 F consumer, no F intermediate or orchardist<br>No specific data reported for M lung cancer. | Average concentration of urinary arsenic ranged from 56 to140 µg/L | No significant increase in lung cancer or all cancers mortality in Intermediates or Orchardists compared to the Consumers. |
| Valberg et al. 1998 | Nevada, Alaska, Utah | Pooled analysis | Study populations from publications (Vig et al. 1984, Harrington et al. 1978, Southwick et al. 1983) on communities with high drinking water arsenic levels | Used the current EPA arsenic cancer slope factor (CSF) to predict the expected number of skin cancers given that zero skin cancers were observed. | 76-401 µg/L | Null hypothesis of no additional skin cancer risk from arsenic was approximately 2.2 more times likely than the hypothesis that ingested arsenic causes the rate of skin cancer predicted by the CSF. |
| **Communities near Smelters/Industrial Facilities** | | | | | | |
| Tollestrup et al. 2003 | Ruston/Tacoma, Washington | Cohort | Individuals born between 1895 and 1925 who had resided in the study area (within 2.0 miles of the copper smelter) for at least 2 years prior to age 14 between 1907 and 1932. N=3,336 potential participants, 196 who later worked at the smelter were excluded. Eight additional excluded because born prior to 1895 or after 1925. Follow-up through December 31, 1990. | Total N=3,132 (1,827 boys, 1,305 girls)<br>Malignant neoplasms, M: 121, F: 88<br>Lung cancer, M: 47, F: 15<br>Bladder cancer, M: 4, F: 1 | Not reported in study. In the 1970s and early 1980s with air pollution controls, air levels averaged 0.8 µg/$m^3$ with an occasional elevation to 10 µg/$m^3$ (Frost et al. 1987; Milham 1988). Speciated urinary arsenic levels in children in the early 1980s averaged 52 µg/L (Polissar et al. 1987). Historical levels would have been even higher. | "No consistent patterns of adverse health effects, including excess mortality rates from lung and bladder cancer." (p. 626). |

**Attachment 1. (cont.)**

| Reference | Study Location | Study type | Study Population (Exposed) | Sample Size and Number of Observed or Exposed | Range of Arsenic Exposure Levels | Study Findings |
|---|---|---|---|---|---|---|
| Frost et al. 1987 | Ruston/Tacoma, Washington | Case control and Ecological | Identified lung cancer deaths between 1935–1969 occurring in women residing near copper smelter. N=164. Cases and controls were restricted to residents with either a Tacoma or Ruston address as determined by death certificate. | Case control study:<br>156 cases; 156 controls<br>Ecological study:<br>Ruston area N=36<br>Remainder of Tacoma N=125<br>Remainder of Pierce County N=100 | Not reported in study. In the 1970s and early 1980s with air pollution controls, air levels averaged 0.8 µg/$m^3$ with an occasional elevation to 10 µg/$m^3$ (Frost et al. 1987; Milham 1988). Speciated urinary arsenic levels in children in the early 1980s averaged 52 µg/L (Polissar et al. 1987). Historical levels would have been even higher. | Case-control study:<br>"An elevated incidence of lung cancer was not detected in comparing observed with expected lung cancer rates." (p. 151) Odds ratio of 1.58 for highest exposure index; trend not significant (P=0.07).<br>Ecological study:<br>Relative risk of 0.94 with upper one-sided 95% CI of 1.08 |
| Greaves et al. 1981 | Idaho (zinc smelter) and Montana, New Mexico, Utah, Arizona (6 sites) (all copper smelters) | Case control | Lists of cancer patients were obtained from state cancer registries (Idaho, New Mexico, and Utah); from local hospitals (Montana); or lists were abstracted from death certificates (Arizona) for those within a 20-km radius of smelter 1970-1977. | 71 cases<br>158 controls | Examined distribution of cases and controls with respect to distance from smelters. Exposure levels not given. Arsenic levels in ore highest in Montana, intermediate in Utah, and lowest in Arizona. The arsenic level in soil 1.1 km from smelter in Utah was 540 ppm. | "Lung cancer cases did not live closer to the smelter than the controls at any of the sites." (p. 17) |
| Lyon et al. 1977 | Salt Lake City, Utah | Case control | Identified new cases of lung cancer in 1969-1975 within 25 miles of smelter. | 593 cases (479 M; 114 F)<br>265 controls (153M; 112 F) | Association examined with distance from smelter. Sulfur dioxide and arsenic emissions noted but no arsenic levels given. | "No association between lung cancer incidence and residence near a smelter." (p. 869) |
| Marsh et al. 1997 | 6 copper smelter towns in Arizona | Case control | Identified as all lung cancer deaths between 1979-1990 (based on residence at time of death listed on death certificate). N=183 | 150 cases<br>322 controls | Not given. Arsenic exposure based on occupational studies and ore content appears low, but historical exposures could have been higher in the past when less air pollution controls were used. | No association between lung cancer mortality and residential exposure to smelter emissions. "Among male residents of some, but not all, towns, there was some evidence of a positive association between lung cancer risk and reported copper smelter-related employment." (abstract) |
| Marsh et al. 1998 | 4 copper smelter towns in Arizona | Case control | Identified as all lung cancer deaths between 1979-1990 in 4 smelter towns and a 25-km radius surrounding the town (based on residence at time of death listed on death certificate). N=142 | 114 cases<br>210 controls | Not given. Arsenic exposure based on occupational studies and ore content appears low, but historical exposures could have been higher if ore content differed in the past when less air pollution controls were used. | "This study provided little evidence that lung cancer mortality risk among residents of these smelter towns was associated positively with general environmental (residential) exposures to smelter emissions." (p. 26) |

**Attachment 1. (cont.)**

| Reference | Study Location | Study type | Study Population (Exposed) | Sample Size and Number of Observed or Exposed | Range of Arsenic Exposure Levels | Study Findings |
|---|---|---|---|---|---|---|
| Pershagen 1985 | Near Ronnskarsverken copper smelter in northern Sweden | Case control | Two parishes in one county chosen as the exposed area; the remaining part of the county constitutes the reference area. Cases were identified as men who died between 1961 and 1979 with a diagnosis of carcinoma of the bronchus, lung or pleura in the study area. Six additional cases were identified from the National Register on Causes of Death and the regional cancer register. N=221 | 42 cases in the community who were not miners or smelter workers (4 non-smokers and 38 smokers) matched to 55 controls (25 nonsmokers and 30 smokers) | Not given | Increased relative risk of lung cancer in smokers residing in the exposed area compared to the reference area (RR=2.2; 95%CI=1.3-3.9). Relative risk for nonsmokers were similar but not statistically significant. |
| Rom et al. 1982 | El Paso, Texas | Case control | Cases were collected from death certificates and hospital charts (1944-1949) and incidence data (1950-1973) collected at time of diagnosis. | 575 cases (413 M: 162 F) 1,490 controls (376 M; 1,114 F) | Arsenic containing ore used. Smelter in continuous operation since 1887. Exposure examined with respect to distance from smelter. Six-month mean levels of arsenic in air in 1972 ranged from 2.5 µg/$m^3$ at the property boundary to <0.05 µg/$m^3$ 3-5 km from the smelter | No association was found between lung cancer and distance from the El Paso smelter compared with control cancers for the period 1944-73 for 575 cases and 1,490 controls. (p. 270) |
| Cordier et al. 1983 | Quebec Province (Rouyn-Noranda) | Ecological | All deaths in Rouyn-Noranda between 1965-1975: N=1,733. Total population 1971 N=28,555 | Rouyn-Noranda (cases)<br>Malignant neoplasms, M:225, F:124<br>Lung, M:71, F:7<br>Val D'or (comparison)<br>Malignant neoplasms, M:114, F:69<br>Lung, M:27, F:5<br>Quebec province (comparison)<br>Malignant neoplasms, M:48,590, F:39,030<br>Lung, M:12,950, F:2,100 | Not given. The authors report estimates for sulfur dioxide and lead, but not arsenic. | Mortality patterns in Rouyn-Noranda show a statistically significant excess of deaths by lung cancer in men (SRR =1.53 vs. Val D'or; SRR = 1.22 vs. Quebec) but not women. Evidence of increases in chronic respiratory disease in both men and women. |

## Attachment 1. (cont.)

| Reference | Study Location | Study type | Study Population (Exposed) | Sample Size and Number of Observed or Exposed | Range of Arsenic Exposure Levels | Study Findings |
|---|---|---|---|---|---|---|
| Matanoski et al. 1981 | Arsenical pesticide plant, Baltimore, Maryland | Ecological | Cancer death rates for 4 index census tracts during 1958-1962 and 1968-1974 compared to controls. Included only deaths occurring inside the city. | Population for each census tract not provided.<br>Number of cases for 4 index tracts (1958-1962):<br>All cancers, M: 95, F: 52<br>Lung, M: 29, F; 1<br>Number of cases for 4 index tracts (1968-1974):<br>All cancers, M: 127, F: 73<br>Lung, M: 62, F: 8<br>Number of cases for 3 index tracts (1958-1962 and 1966-1974):<br>All cancers, WM: 184, WF: 98<br>Lung, WM: 78, WF: 6<br>Bladder, WM: 5. WF: 0 | Soil sampling conducted near plant, in area farther out to determine how distant elevated levels could be detected, and in two distant parks, as controls.<br>Tract 2303, Mean= 63 ppm<br>Tracts 2301 and 2404, Mean= 6 ppm<br>Tract 2302, Mean= 4 ppm | In Tract 2303 ( the tract with the highest soil levels), there was significantly increased mortality for men (lung cancer [SMR=2.74] and all cancer [SMR=1.94]) but not for women, for the 1958-1962 and 1966-1974 time periods.<br>Of the cases with known smoking history 30 men were smokers and 2 men were nonsmokers. Removing 4 cases who were employed at the plant did not change the significance of the rate. |
| Wong et al. 1992 | Four counties in Montana | Ecological | All histologically confirmed skin cancer cases during the period January 1980 through June 1986 were collected from pathology services and dermatologists in Deer Lodge (with former Anaconda copper smelter) and Silver Bow (Butte open pit copper mine and smelter) counties. Gallatin and Park Counties used as controls. | 2,252 skin cancer cases identified by NCI case definition<br>2,451 skin cancer cases identified by "study" definition of case | Not given; but likely substantial for smelter sites. Study areas included the Anaconda and Butte Superfund sites. Elevated urinary arsenic levels were measured in children in the past in Anaconda (Hwang et al. 1997). | "Based on the findings in this study, residents in the exposed counties of Deer Lodge and Silver Bow did not experience an increase in skin cancer incidence as compared to the residents in Gallatin and Park counties." (p. 241) |

**Note:**
BCC - basal cell carcinoma
CI - confidence interval
CSF - cancer slope factor
EPA - Environmental Protection Agency
F - female
M - male
N - number
NCHS - National Center for Health Statistics
NCI - National Cancer Institute
OR - odds ratio
RR - relative risk
SCC - squamous cell carcinoma
SMR - standardized mortality ratio
SRR - standardized rate ratio
WF - white female
WM - white male

## Attachment 2

# Derivation of Risk Estimates with Current and Proposed Cancer Slope Factor

**Attachment 2. Derivation of risk estimates with current and proposed cancer slope factor (CSF)**

| Parameter | Risks Related to Diet and Water[a]: Mean Diet and Water ≤10 μg/L | Risks Related to Diet and Water[a]: Mean Diet and Existing Water | Risks Related to Diet and Water[a]: Risks Related to Diet and Water at 90th Percentile | Risks Related to Water[b] | Risks Related to Direct Contact with Soil[c] | | |
|---|---|---|---|---|---|---|---|
| Intake in μg/day | 5.6 | 6.1 | 10.5 | -- | -- | -- | -- |
| Assumed water concentration mg/L | -- | -- | -- | 0.01 | -- | -- | -- |
| Soil concentration mg/kg | -- | -- | -- | -- | 20 | 50 | 100 |
| Intake in mg/kg-day | 8.0.E-05 | 8.7.E-05 | 1.5.E-04 | 2.9.E-04 | -- | -- | -- |
| Conversion factor (mg/μg) | 1.0.E-03 | 1.0.E-03 | 1.0.E-03 | -- | -- | -- | -- |
| Daily lifetime water intake (L/day) (U.S. EPA 2005) | -- | -- | -- | 2 | -- | -- | -- |
| Adult body weight (kg) (U.S. EPA 1991) | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Lifetime (70 years*365 days) | -- | 25,550 | 25,550 | 25,550 | 25,550 | 25,550 | 25,550 |
| Exposure frequency (days/year) | **365** | **365** | **365** | **365** | **365** | **365** | **365** |
| Exposure duration (years) | **70** | **70** | **70** | **70** | **30** | **30** | **30** |
| Current CSF–Carcinogenic potency factor for arsenic, mg/kg-day$^{-1}$ | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Proposed CSF–Carcinogenic potency factor for arsenic, mg/kg-day$^{-1}$ | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 | 5.7 |
| Soil ingestion rate (mg/day) child (U.S. EPA 1991) | -- | -- | -- | -- | **200** | **200** | **200** |
| Soil Ingestion rate (mg/day) adult (U.S. EPA 1991) | -- | -- | -- | -- | **100** | **100** | **100** |
| Oral absorption from soil (unitless) | -- | -- | -- | -- | 0.8 | 0.8 | 0.8 |
| Integrated term for soil ingestion (mg-year/kg-day) | -- | -- | -- | -- | 114 | 114 | 114 |
| Conversion factor mg per kilogram (unitless) | 1E-06 | -- | -- | -- | 1E-06 | 1E-06 | 1E-06 |
| Dermal surface area (cm$^2$/day) adult (U.S. EPA 2004) | -- | -- | -- | -- | 5,700 | 5,700 | 5,700 |
| Dermal adherence (mg/cm$^2$) adult (U.S. EPA 2004) | -- | -- | -- | -- | 0.07 | 0.07 | 0.07 |
| Dermal surface area (cm$^2$/day) child (U.S. EPA 2004) | -- | -- | -- | -- | 2,800 | 2,800 | 2,800 |
| Dermal adherence (mg/cm$^2$) child (U.S. EPA 2004) | -- | -- | -- | -- | 0.2 | 0.2 | 0.2 |
| Dermal absorption from soil (unitless) (U.S. EPA 2004) | -- | -- | -- | -- | 0.03 | 0.03 | 0.03 |
| Integrated term for soil dermal (mg-year/kg-day) | -- | -- | -- | -- | 361 | 361 | 361 |
| | Mean Diet and Water ≤10 μg/L | Mean Diet and Existing Water | 90th Percentile Diet and Water | Lifetime Water Intake 10 μg/L | Soil at 20 mg/kg | Soil at 50 mg/kg | Soil at 100 mg/kg |
| Excess lifetime cancer risk at current CSF 1.5 (mg/kg-day)$^{-1}$ | 1.E-04 | 1.E-04 | 2.E-04 | 4.E-04 | 4.E-05 | 1.E-04 | 2.E-04 |
| Excess lifetime cancer risk at proposed CSF 5.7 (mg/kg-day)$^{-1}$ | 5.E-04 | 5.E-04 | 9.E-04 | 2.E-03 | 2.E-04 | 4.E-04 | 8.E-04 |

[a] Dietary and water risk = ($As_{in}$ dietary and water intake μg/day × 0.001 mg/μg x CSF) / 70 kg body weight

[b] Water risk = (mg/L $As_{in}$ water concentration × liters per day × CSF) / 70 kg body weight

[c] Soil contact risk = ($As_{in}$ soil concentration mg/kg × $10^{-6}$ kg/mg x exposure frequency in days x ((integrated soil ingestion term ([mg-year]/[kg-day]) × absorption from soil)
+ (soil integrated dermal contact with soil term × dermal absorption from soil ([mg-year]/[kg/day]))) × CSF) / lifetime averaging time in days

- Integrated soil ingestion term = ((100 mg/day adult intake × 24 years adult exposure) / 70 kg adult body weight) + ((200 mg/day child intake × 6 years child exposure) / 15 kg child body weight ).
- Integrated dermal contact term = ((5,700 cm$^2$ adult surface area × 0.07 mg/cm$^2$ adult adherence × 24 years adult exposure) / 70 kg adult body weight) + ((2,800 cm$^2$ child surface area × 0.2 mg/cm$^2$ child adherence × 6 years child exposure) / 15 kg child body weight)

## Attachment 3

## Dooley et al. (2004)

# ESTIMATING A RELATIVE SOURCE CONTRIBUTION FOR DRINKING WATER IN ARSENIC (As) RISK ASSESSMENTS*

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## Abstract

In 1996, the United States Environmental Protection Agency (EPA) charged the National Academy of Sciences/National Research Council (NRC) to review the Agency's draft risk assessment of As in food and drinking water, considering the available studies. The NRC issued a report in 1999, and EPA used many of the NRC's recommendations and data to quantify bladder and lung cancer risks for its 2001 arsenic drinking water regulation. After publishing the final arsenic rule on January 22, 2001, the Agency asked the NRC to re-evaluate the Agency's risk assessment, recent studies, and the effect of data uncertainties and differences in populations related to As. One uncertainty examined is water consumption. The 2001 NRC report commented on the Taiwanese water consumption rates applied in the 1999 NRC report and EPA's 2001 drinking water risk assessment and characterization. In this paper, we use U.S. Army data to examine some parameters that can affect water consumption to estimate drinking water consumption in Taiwan. We used temperature and relative humidity to establish heat categories, along with three different levels of work (light, medium or heavy activity) to estimate the historical water intake levels for Taiwanese (adjusted to 55 kg for males and 50 kg for females). During the warm growing season, water intake estimates ranged from 4.3 L/day (light activity) to 6.4 L/day (medium to heavy activity). During the cooler months, the lower bound estimates were taken from the Army's minimum recommendations of 1.9 to 2.4 L/day. Estimations of water needs were based on only "working" hours and average monthly temperatures. For most of the year, Taiwanese water intake is near 2 L/day, but during the growing season, it may reach 6.4 L/day, for an annual average of 3.6 L/day, approximately the rate used by EPA in its 2001 risk assessment. This methodology needs to be further validated prior to its use in risk assessments.

## Introduction

While most cancer risk assessments are based on animal studies, those for arsenic (As) arise from human epidemiology studies (USEPA, 2001; NRC, 1999; NRC, 2001). The studies used for promulgation of the Agency's 2001 Maximum Contaminant Level (MCL) for As of 10 µg/L (or 10 ppb) (66 FR 6975 (USEPA, 2001)) were derived from studies of Taiwanese people exposed to As in their drinking water supplies. In those studies, it was assumed that the average Taiwanese male weighed 55 kg and the average female was 50 kg. It was also assumed that their mean consumptions of drinking water per day were 3.5 and 2.0 L/day, respectively (66 FR 6975 (USEPA, 2001); NRC, 1999; NRC, 2001). These values can be traced back to the values used by the Agency in its 1988 report on the quantitation of skin cancer in southwest Taiwan (USEPA, 1988).

This level of drinking water consumption has been disputed in a report by Mushak and Crocetti (1995). They used data from Guthrie (1983), and calculated that the average Taiwanese doing light to moderate work would require between 1.9 and 2.1 L/day of water and that approximately one-half of their water intake would be derived from food. There have been several studies which examine water intakes and losses (Table 1). However, direct comparison is difficult because of the many factors that should be considered when estimating water intakes and losses, including: body weight, temperature, humidity, and activity level. For example, data from Guyton et al. (2000, as cited in Berardi, 2001) estimates that a 55 kg person (scaled down from 70 kg) could lose from 1.2 L/day (urine and sweat) at 68 °F with no physical activity, and up to 4.3 L/day (urine and sweat; Table 1) with exercise at 86 °F. Accordingly, we were interested in examining various parameters and estimating drinking water consumption under different conditions throughout the year.

*The opinions expressed in this presentation are those of the authors and do not necessarily represent the opinions or views of the EPA or of the Cadmus Group, Inc.

Presented at the Society of Toxicology Annual Meeting 2004
Abstract published in: 2004 The Toxicologist. 78(S-1): 150.

| Table 1. Comparison of Water Intake Needs and Water Losses | | | | | |
|---|---|---|---|---|---|
| Study | Range of Estimates | Assumptions (where specified) | | | |
| | | *Weight* | *Activity* | *Climate* | *Other* |
| **Water Intake Needs** | | | | | |
| Mushak and Crocetti, 1995 | 0.95 L/day | 50 kg (woman) | inactive | 100°F | 38 ml of water per kg of body weight; 50% of water intake comes from food consumed |
| | 1.05 L/day | 55 kg (man) | active | | |
| NAS, 1980, as cited in NAS, 1989 | 1.2 L/day | 55 kg | | | Scaled down from a 70 kg adult who is not sweating (1.5 L/day) |
| NAS, 1989 | 2-3 L/day | | | | 1.0 to 1.5 ml/kcal and 2,000 kcal/day |
| Downey and Hopkins, 2001 | 0.38 - 0.9 L/hr | 55 kg | extremely high activity (triathalon) | | Scaled down water intake of 52 men and 7 women in triathalon, average mass 72 kg +/- 5 ml/kg/hr |
| **Water Losses** | | | | | |
| Gisolfi et al., 1977 as cited in NAS, 1993 | 0.25 L/hr | | walking 3.5 mph; moderate exercise | 80.6°F dry | 4 endurance runners, weight not specified |
| | 0.7 L/hr | | | 98.6°F humid | |
| Kleiner, 1999 | 1 - 2 L/hr sweat | | moderately heavy exercise | | |
| Guyton et al., 2000, as cited in Berardi, 2001 | 1.1 L urine & <0.1 L sweat/day | 55 kg | no exercise | 68°F | Scaled from a 70 kg person |
| | 0.9 L urine & 1.1 L sweat/day | | no exercise | 85°F | |
| | 0.3 L urine & 4 L sweat/day | | no exercise | 85°F | |

## U.S. Military Water Intake Recommendations

It is of utmost importance to the U.S. Armed Forces to supply its troops with sufficient water to maintain hydration. To accomplish this, they must determine how much drinking water is required to be transported and stocked to prevent dehydration in soldiers at different levels of activity in various climates (e.g., deserts, tropics, mountains). The concept of the wet bulb globe temperature (WBGT) is credited to Navy-commissioned studies of heat effects on exercise safety, which were conducted following heat stroke casualties in the early 1950s experienced by Marines training at Parris Island, South Carolina (Zunis, 1999). The WBGT index became an international standard in 1989 (ISO 7243).

**Equation 1:**

$$WBGT = 0.7\,WB + 0.2\,GT + 0.1\,DB$$

Where:

**WB** - Wet Bulb (Thermometer wrapped in water-soaked cotton to simulate sweat evaporation while exposed to wind and sun)

**GT** - Global Thermometer (Thermometer inside a 6" black ball to consider effects of radiant heat)

**DB** - Dry Bulb (Standard Dry bulb thermometer)

The Occupational Safety and Health Administration (OSHA, 1999) describes the WBGT as a technique to correlate deep body temperature and other physiological responses to heat, wind, sun, and humidity. When a person exercises, muscles release heat energy. A liter of sweat releases 580 Kcal of heat to the air when it evaporates from the skin. However, when the air is humid, less sweat evaporates (Zunis, 1999). The U.S. military developed hourly water intake rates based on activity level, and

**Table 2. Work/Rest Cycles and Water Consumption Rates**

| Heat Category [1] | WBGT Index °F | Easy Work [2] | | Moderate Work [2] | | Hard Work | |
|---|---|---|---|---|---|---|---|
| | | Work/Rest (min) | Water Intake (Qt/hr) | Work/Rest (min) | Water Intake (Qt/hr) | Work/Rest (min) | Water Intake (Qt/hr) |
| 1 (White) | 78° - 81.9° | NL | 1/2 | N/L | 3/4 | 40/20 | 3/4 |
| 2 (Green) | 82° - 84.9° | NL | 1/2 | 50/10 | 3/4 | 30/30 | 1 |
| 3 (Yellow) | 85° - 87.9° | NL | 3/4 | 40/20 | 3/4 | 30/30 | 1 |
| 4 (Red) | 88° - 89.9° | NL | 3/4 | 30/30 | 3/4 | 20/40 | 1 |
| 5 (Black) | >90° | 50/10 | 1 | 20/40 | 1 | 10/50 | 1 |

Reference: Martin Army Community Hospital (http://www.martin.amedd.army.mil/wet_heat_web.html); also available at: U.S. Army Center for Health Promotion and Preventive Medicine 2002 Heat Stress Card http://usachppm.apgea.army.mil/doem/pgm34/HIPP/WorkRestTable.pdf) and (http://chppm-www.apgea.army.mil/doem/pgm34/hipp/heat%20stress%20card.pdf).

[1] Color coded flags, as indicated in parentheses, are used at U.S. military bases as a notification of daily water intake needs.
[2] NL = no limit to work time per hour.

using the WBGT (see Equation 1) method. The recommendations for troops in battle dress (e.g., long sleeves, packs, etc) are presented above in Table 2 (from: http://www.martin.ammed.army.mil/wet_heat_web.html).

The Martin Army Community Hospital Web site also provides a table linking the five heat categories to air temperature and relative humidity values. This is a practical tool for estimating water intake needs, because WBGT data are often not available; and in fact, were not available for southwestern Taiwan. Historic temperature and humidity data are available through the Taiwan Central Weather Bureau Web site (http://www.cwb.gov.tw) from 1961 to 1990 for the town of Chiayi, Taiwan, a moderately sized community in the middle of the southwestern Taiwan region. We used this data in Figure 1 to estimate the relevant water intake needs.

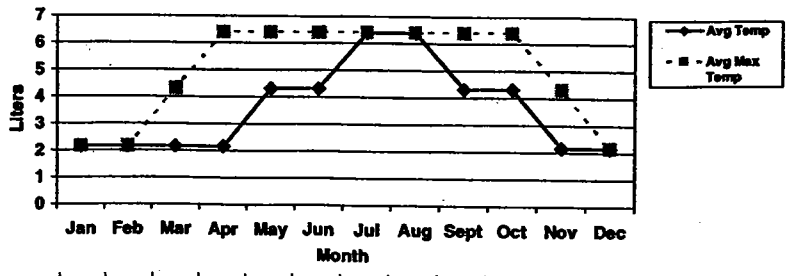
## Results

Using the U.S. military data, we estimated water consumption, in liters per day for each month of the year, using a moderate activity level, and the average temperature and relative humidity (Figure 1). The military guidelines in Table 2 were adjusted downward by 1/4 L/hour to account for the lower average body weight of the Taiwanese (as compared to the average weight of a U.S. soldier). To convert from "per hour" to "per day", we assumed that their primary water needs occurred during working hours and multiplied the hourly rate by 9 hours/day. The calculation used was as follows:

**Equation 2:**

**Average Daily Water Intake** = (9 hrs/day) *x* (military per hour intake recommendations) *(adjusted for body weight differential)*.

**Figure 1. Climate Data for Chiayi, Taiwan (1961-1990) and Corresponding Water Intake Needs for Moderate Activity Level**




| | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sept | Oct | Nov | Dec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relative Humidity (%) | 83 | 85 | 85 | 86 | 86 | 84 | 82 | 85 | 87 | 86 | 83 | 81 |
| Heat Category | 0/0 | 0/0 | 0/1 | 0/5 | 2/5 | 4/5 | 5/5 | 5/5 | 3/5 | 1/5 | 0/3 | 0/0 |

*NOTE:* These data represent Taiwan's Central Weather Bureau's (CWB) Observatory monthly averages for Chiayi from 1961-1990 (http://www.cwb.gov.tw/V4e/index.htm).

| Table 3. Hourly Temperatures (°F), Kaohsiung, Taiwan, December 15, 2003 (www.wunderground.com/history) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Time am* | 12:00 | 1:00 | 2:00 | 3:00 | 4:00 | 5:00 | 6:00 | 7:00 | 8:00 | 9:00 | 10:00 | 11:00 |
| *Temp.* | 59.0 | 59.0 | 57.2 | 57.2 | 55.4 | 57.2 | 55.4 | 57.2 | 59.0 | 64.4 | 68.0 | 69.8 |
| | | | | | | | | | | | | |
| *Time pm* | 12:00 | 1:00 | 2:00 | 3:00 | 4:00 | 5:00 | 6:00 | 7:00 | 8:00 | 9:00 | 10:00 | 11:00 |
| *Temp.* | 71.6 | 71.6 | 71.6 | 69.8 | 69.8 | 68.0 | 68.0 | 68.0 | 66.2 | 66.2 | 64.4 | 62.5 |

The highest intakes would be in August (given high average temperatures and work in rice fields), when estimated water needs could exceed 6 L/day. However, the annual average daily water intake for a moderately active worker in southwestern Taiwan would be 3.6 L/day. If estimates were based on average maximum monthly temperatures, the annual average would be 5 L/day (Figure 1). Average monthly (diurnal) temperatures tend to underestimate the temperature during the working hours, as noted in the discussion of Table 3.

The average daily temperature for a recent day in Kaohsiung, Taiwan, a community just south of Chiayi, was 64.0 °F, which compares favorably to the 1961-1990 average temperature in Chiayi (Table 2) for December of 63 °F. The average daily temperature in Kaohsiung between 7 am and 4 pm is 67.3 °F.

## Conclusions

Applying the U.S. military water intake guidelines to historical Taiwanese weather data appears to support the daily water consumption rate of 3.5 L/day for the Taiwanese which EPA used in its 2001 risk assessment. We used the following factors:

(1) A moderate level of activity to adjust for annual variations in workloads.

(2) Calculated water consumption for a work day of 9 hours, which does not account for food and drink ingested during the rest of the day.

There are two other factors which could affect these calculations:

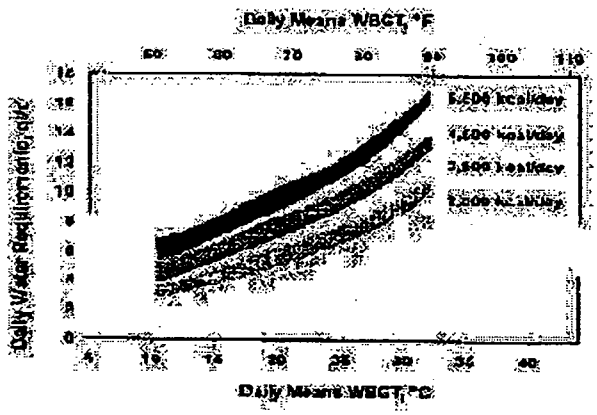
(1) WBGT heat categories, based on battle dress, probably overestimate water requirements of the Taiwanese.

(2) Calculating Taiwanese heat categories from average daily (diurnal) temperatures may underestimate water requirements.

At the present time, we cannot quantify these effects.

Other U.S. military estimates illustrate and support the conclusions of this paper. Figure 3-5 from the Army 2003 bulletin (AFPAM, 2003) derives daily water requirements at different daily mean WBGT temperatures at different caloric (energy) expenditures. This figure uses the average temperature during the day (not 24-hour average temperature) and assumes that the work is done during the day. The top of each curve is for work done in full sun and the bottom of each curve is for work done in the shade.

**Figure 3.5. Daily water requirements during various daily climatic (day time average WBGT) and metabolic (kcal/d) conditions**



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## Attachment 4

## Abernathy et al. (1989)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

2/23/89

OFFICE OF WATER

MEMORANDUM

Subject: Report on Arsenic (As) Work Group Meetings.

From: Charles O. Abernathy (Reporter)
William Marcus
Office of Drinking Water

Chao Chen
Herman Gibb
Paul White
Office of Research and Development

To: Peter Cook
Deputy Director,
Office of Drinking Water (WH-550)

Peter Preuss
Director,
Office of Regulatory Support
and Scientific Management (RD-672)

I. Introduction.

C. Chen, H. Gibb, P. White of ORD and W. Marcus (telephone) and C. Abernathy of ODW met on several occassions to discuss the Tseng (1968, 1977) and Southwick et al. (1983) studies, the ORD trip (Irgolic, 1988 report and other relevant As publications and reports in order to try to reach some conclusions on which study to use for calculating an RfD for As. The adverse effects considered by the Work Group for establishing a NOAEL were hyperkeratosis and Blackfoot Disease. Specific comments by individuals will be attributed to those individuals.

It was generally agreed that, although there were a lot of facts, the data were scattered and there were serious data gaps. The paucity of data in many areas prevented the group from reaching definitive conclusions. The discussion centered around the amount of water (direct and indirect) ingested, the amount of food (rice and sweet potatoes) eaten, the levels of As in food, water and soil, uptake of As from the soil by plants and the percent of As as inorganic As in food and water. The analyses presented below will be based on various assumptions which will be specified.

II. Water Consumption.

A. Direct. The value of 3.5 l of water/day was used for the ORD calculations.

1. H. Gibb talked to 3 to 4 people in Blackfoot treatment center and asked them to estimate their water consumption. They estimated that they drank up to three 1.25 l bottles of water per day. Since he had to ask the questions through an interpreter and only a limited number of persons were asked, H. Gibb felt that the data were a little "soft" and could only be used as an approximation, but that they were consistent with the view of the Work Group on water consumption by the Taiwanese.

2. P. White agreed that the information on Taiwanese water consumption was limited. He felt that the Taiwanese laborers could have had higher fluid consumption than the general U. S. population, but noted that; this water consumption applies to the entire population (laborers and nonlaborers) over the whole year, Taiwanese are physically smaller than average Americans, and U.S drinking water consumption tends to be less than 2 l/day. Therefore, he did not feel confident that water consumption was as high as 3.5 l/day and felt that 3.5 l/day might be an appropriate estimate of total water consumption (see below).

3. Chao Chen, W. Marcus and C. Abernathy felt that in a warm to hot climate, laborers could easily drink 3 to 4 l of water/day.

Most of the workgroup felt that the Taiwanese workers could drink 3 to 4 l of water/day and that 3.5 l/day seemed to be a reasonable estimate for direct water consumption.

B. Indirect. Water was used to cook rice and sweet potatoes and this amount was not factored into the original exposure scenario.

1. Rice. C. Abernathy mentioned the fact the J. Du (ODW) had cooked rice and found that it took approximately 200 ml of water to cook 100 g of rice. This value was accepted by the workgroup.

2. Sweet potatoes. They are eaten either as fresh vegetables or are sun-dried for preservation in order to eat them during nongrowing seasons. The dry form of the vegetable would take more water (The rice and sweet potatoes are cooked together - Chao Chen.) to cook than the fresh form. Taking into consideration the dry and the fresh forms, Chao Chen estimated that it would take 50 to 75% as much water to cook the sweet potatoes as it would to cook the rice. Accodingly, if we assume that it would take 63% as much water for the potatoes as the rice, then for 100 g of potatoes, it would take 125 ml of water (200 ml x 63% = 125 ml).

C. As levels in water. In the NOAEL group (approximately 2,500), there is an exposure range of 1 to 17 ug As/liter of drinking water (Tseng, 1977). Chien-Jen Chen of the National Taiwan University of Taipei, Taiwan (telephone call) thought that more of the exposed people were in the low dose range, but had no data. The As Work Group concluded that an accurate scientific estimate would be difficult to make on the basis of the present data.

III. Food Consumption.

A. Total food. From Table 1 in the Irgolic (1988) report (p. 5), rice and sweet potatoes account for 90% (750 g) of the food intake by this population. Accordingly, only these two sources of food will be considered in the food exposure analysis. The relative proportions of rice and sweet potatoes would vary with the economic status of the families. Irgolic (p. 4) states that the poorer families would eat more and, sometimes exclusively, sweet potatoes, while the more prosperous families would eat more rice.

1. Rice. Chao Chen stated that the endemic study area was very poor and that rice consumption would be below the 376 g average (Irgolic, 1988). It was estimated by the workgroup that 200 to 250 g of rice would be consumed/day.

2. Sweet potatoes. It was estimated that this population would consume 500 g of sweet potatoes (Greater than the 360 g average given by Irgolic, 1988.).

IV. Analysis. Variables will first be discussed separately and then combined in the next section to provide different exposure scenarios.

A. Water.

1. Direct. 3.5 l (from a range of 3 to 4 l).

2. Indirect. Cooking water.
   a. Rice. 225 g X 200 ml/100 g = 450 ml.
   b. Sweet potatoes. 500 g X 125 ml/100 g = 625 ml.
   c. Total indirect. 450 ml + 625 ml = 1 liter (appr.)

B. Food.

1. Rice. 225 g/day (Section III.A.1).

2. Sweet potatoes. 500 g/day (Section III.A.2).

C. Arsenic levels.

1. Water. In the 7,500 control population, approximately 5,000 were from the island of Matsu and they were exposed to virtually no As directly from their drinking water. There were approximately 2,500 control subjects in the endemic area who were exposed to 0.001 to 0.017 mg As/l (1 to 17 ug/l) in their drinking water. This 2,500 is the NOAEL population used in this report.

a. P. White thought that it should be limited to men which would bring the exposed population below 2,500, since women might receive lower exposures due to decreased water and food consumption. He and Chao Chen also noted that a relatively small fraction of the population actually had lifetime exposures.

b. H. Gibb thought that an average exposure value of 9 ug/l should be the maximum used for the NOAEL calculations.

c. C. Abernathy and W. Marcus felt that 17 ug/l should be included in the calculations, since it would give a maximum exposure scenario for drinking water.

d. Chao Chen said that he believed that very few of the 2,500 would have been exposed to the 17 ug/l level and for that reason believed that the average value of 9 ug/l or a geometric mean of 4 ug/l should be used. The committee reached agreement on an exposure range of 4 to 9 ug As/l of drinking water, believing it to be the best estimate that could be reached with the availible data set.

To demonstrate the potential scope of As exposure from As in the drinking water will be calculated using 1, 4, 9 and 17 ug/l (See Tables 1, 2 and 3 on p. 12).

2. Food.

a. Rice

1). On p. 5, Irgolic (1988) gives a range of less than 0.07 up to 3.5 ug of As/g of rice (70 to 3,500 ug/kg) for rice grown in soils not contaminated with As-herbicides. However, he does not give any specific data on how this range applies to the rice consumed by the Taiwanese population. Consequently, the workgroup did not use this range in the calculations.

2). Irgolic (1988) states on p. 5 that soils in the endemic area contaminated with As-herbicides are "said" to contain approximately 8 mg As/kg of soil, while uncontaminated soils have "natural" levels of 0.1 to 40 mg As/kg (average of 5 mg As/kg). He also cited a study which reported that hulled rice grown in soil containing 20 mg As/kg (as sodium arsenate) had As levels of 0.11 mg As/kg of rice. He caveated this figure by stating that without knowledge of soil characteristics, it would be impossible to estimate, with confidence, how much As would be taken up from the soil. Since there were no data available on types of soil or on the forms of As present in the soil, we based our analysis on the assumption that all forms of As in all types of soil would be concentrated by rice at rates similar to the 0.11 mg As/kg of rice in the rice grown in the soil containing 20 mg As/kg. Therefore, the Work Group adopted the following estimates:

a). Natural soil. 5 mg As/kg is 0.25 of 20 mg As/kg
0.25 X 0.11 mg = 30 ug As/kg rice
(rounded from 28 ug)

b). Contaminated soil. 8 mg As/kg is 0.40 of 20.
0.40 X 0.11 mg = 40 ug As/kg rice
(rounded from 44 ug)

3). Li et al. (1979) reported As levels in three types of rice grown in Taiwan. The highest level found was greater than 0.760 ppm (760 ug As/kg rice) with an average range of 0.3 to 0.5 ppm. Chao Chen identified an analysis of rice from the general area and it had a range of 0.05 to 0.33 ppm (rounded average of 0.2 ppm or 200 ug As/kg rice). These authors believed that the use of As-herbicides contributed to the level of As in the rice. Chao Chen felt that since the people in the endemic area were very poor, they would not have used any As-herbicides during the exposure period. In addition, a great deal of the exposure occrurred prior to the advent of pesticides.

The above cited values from natural and contaminated soil and from the Li et al. (1979) study will be used to give a range of possible exposure scenarios.

b. Sweet potatoes.

1). Irgolic (1988) gave a value of 0.008 to 1.25 ug As/g sweet potato in Table 1 (p. 5). This value, however is for "other potatoes grown in untreated soils" (p. 6), since the only report that he could find claimed that sweet potatoes did not contain any As. The Work Group found these comments impossible to interpret since As was found in sweet potatoes in the FDA "market-basket" survey of U. S. food cited by OPP (OPP, 1987).

D. Type (Inorganic or Organic) of As in water and food.

1. Water. Irgolic (1988) states the As in water is predominantly in the inorganic form (p. 7). Accordingly, As in drinking water will be assumed to be 100% inorganic.

2. Food. There are no data on the forms of As in the diet of the Taiwanese. The only information that we could find on the percent of inorganic As in food was in the FDA survey of U. S. food (OPP, 1987). This memo puts the percent inorganic As in rice and sweet potatoes at 35 and 5%, respectively.

Unless there are data to show that As levels in Taiwanese sweet potatoes are high or that there is a different percentage of inorganic As in the Taiwanese sweet potatoes, its contribution to the total body burden of the individual would be low. For example, if sweet potatoes contained 200 ug As/kg, the the inorganic As in the diet would be 5 ug (200 ug As/ kg x 0.5 kg of sweet potatoes eaten/day = 100 ug As/day x 5% (% of inorganic As) = 5 ug inorganic As/day.

E. Calculations.

1. Drinking water summary.

a. Direct - 3.5 l/day
b. Indirect - 1 l/day

c. Total - 4.5 l/day
d. % inorganic As - 100
e. As in water - 1, 4, 9 or 17 ug/l

2. Food summary.

a. Rice summary.

1). Using As soil uptake data (20 mg As/kg of soil yields 0.11 mg As/kg rice).
a). Natural soil. 5 mg As/Kg soil.
0.25 X 0.11 mg As/kg = 30 ug As/kg rice
0.225 kg X 30 ug As/kg = 7 ug As/day
7 ug As/day X 0.35 = 2 ug inorganic As/day.

b). Contaminated Soil. 8 mg As/kg soil
0.40 X 0.11 mg As/kg = 40 ug As/kg rice
0.225 kg X 40 ug As/kg = 10 ug As/day
10 ug As/day X 0.35 = 4 ug inorganic As/day.

2) Using Li et al.(1979) study.
a). Average value of 200 ug As/kg rice
0.225 kg X 200 ug As/kg = 45 ug As/day
45 ug As/day X 0.35 = 16 ug inorganic As/day.

b. Sweet potatoes. Not included in calculations since we have no reliable data for calculation.
c. The above data are compiled in Tables 1, 2 and 3 on p. 12.

V. Internal Cancer Data.

C. Abernathy inquired about the possibility of ORD calculating a cancer potency estimate for internal cancers and was informed that the data of Chien-Jen Chen (Taiwan) is not complete and, at this time, can not be used for calculations. W. Marcus asked for a time estimate for completion of this task and H. Gibb and Chao Chen said that, even if the time and money were alloted, it would not be possible to give an estimate since the database is not complete.

VI. Southwick et al. (1983) study.

There were 145 "exposed" participants (cities of Hinckley and Deseret) and 105 control participants (city of Delta) in this study. The "exposed" populations of Hinckley and Deseret had a median As exposure level of 5 ug/kg/day, while the "control" group from Delta had a median As exposure level of 0.7 ug/kg/day. All participants came from Millard County, Utah and lived a "predominantly Mormon" lifestyle.

The authors found a close correlation between the amount of As consumed and the levels of As in urine and hair samples. Although the dermatological abnormalities were higher in the exposed (6.25%) than in the controls (2.86%), the difference between the two populations was not statistically significant.

With respect to neurological findings, the data suggested that there was a slightly increased proportion of people with slower nerve conduction among the exposed population. However, not all of the study participants took part in this section of the study (Controls - 67 and Exposed - 83) and the results were not statistically different. Although this study offers suggestions that As could have affected nerve conduction in the "exposed" group, the data are not conclusive.

Based on the above observations, the exposure level of 5 ug/kg/day could be considered as a NOAEL or LOAEL. However; due to the small population size of the Southwick et al. (1983) study, the uncertainties about the significance of the slightly increased incidence of dermatological abnormalities and of slowing of nerve conduction in the As exposed group, the fact that some participants were on the study for only 5 years and that very few (less than 20) were exposed for 60 or more years, it was concluded by the As Work Group that the Southwick et al. (1983) study should not be used for calculating a RfD.

VII. Uncertainty Factor (UF).

There was a discussion as to what UF should be used with the Tseng (1977) study and ODW and ORD could not reach agreement on this point. Specifically, ORD felt that an UF should be used in calculating a RfD because:

1. Most individuals in the Tseng (1977) and Tseng et al (1968) studies were young and few had As exposures in drinking water approaching lifetime duration. Therefore, the observed absence of skin lesions provides less convincing evidence than would be the case if the entire population had received exposures of lifetime duration. Age-specific

prevalence for hyperkeratosis in the "exposed" of the Tseng studies indicate that the observation of 2,500 "control" individuals (0.001 to 0.017 ppm or 1 to 17 ug As/l in drinking water) would only be one-fourth as effective in detecting skin lesions as would be the case if all the individuals had recieved lifetime duration exposures. Furthermore, due to the As-associated mortality (in particular, blackfoot disease) in the "exposed" Tseng group, the steepness of the age/prevalence relationship for hyperkeratosis may be underestimated. Thus, the above considerations may still overstate the effectiveness of the Tseng study in establishing a NOAEL;

2. The Cebrian et al. (1983) study reported that 7 of 318 "controls" (exposed to 5 ug of As/l of drinking water) had dermatological signs of As exposure. This introduces uncertainty into the Tseng (1977) derived NOAEL of 4 to 9 ug As/l of drinking water as selected by the Work Group;

3. As noted in # 2, the reported findings of adverse effects in the Cebrian et al. (1983) "control" are not concordant with the absence of effects in the Tseng "control" group. This may indicate that the exposure values developed for the Tseng (1977) study are too high. If this is the case, the calculated NOAEL is also an overestimate;

4. Little information exists on the prevalence or incidence of hyperkeratosis in the United States. The fact that a substantial subgroup of the American population may be exposed to drinking water As levels above 50 ug/l does not in itelf provide any reassurance that As-induced lesions are not occurring. Lesions which do occur may not be called to the attention of a physician. Furthermore, reporting of such lesions in the medical literature would likely be sporadic;

5. Comparisons between the UF appropriate for a RfD derived from the Tseng (1977) study with UFs used in previous RfD calculations may be of limited use because;

(a) the reported data from the Tseng studies were not sufficient to construct a dose-response relationship for hyperkeratosis. When data on a compound indicate that a steep dose-response is observed, one may have greater confidence that a study NOAEL is indeed a "safe" level of exposure, and

(b) much of the uncertainty in establishing a NOAEL using the Tseng (1977) study is due to uncertainty in exposure levels. Exposure levels will generally be better known in small experimentally-oriented studies with human subjects.

ODW felt that an UF of 1 should be used because:

1. The Work Group used hyperkeratosis, which may not be an adverse effect, as a toxicological endpoint;

2. The Tseng (1977) population is of sufficient size to use an UF of 1. In this regard, it is of interest to note that other RfD studies in humans, with cholinesterase inhibition as an endpoint

and validated by the Agency's RfD Work Group, having exposure groups of 5 to 10 humans/dose use an UF of 10;

3. Other studies, with smaller populations and higher doses than than the Tseng (1977) study, conducted in the U. S. and Canada, such as Harrington et al (1978) in Alaska, Hindmarsh et al (1977) in Canada, Goldsmith et al (1972) in California, Morton et al (1977) in Oregon, Vig et al. (1984) in Nevada and Southwick et al. (1983) in Utah indicate that exposure to concentrations of As up to 50 ug/l in the drinking water does not produce hyperkeratosis and/or other forms of As toxicity;

4. The exposure of 100,000 people in the U. S. to As levels of 50 ug/l or higher (U. S. EPA, 1987) is compatible to the above studies cited in ¶ 2;

5. The report of 7 of 318 "controls" in the Cebrian et al (1983) study having dermatological signs (hypo- and hyperpigmentation) of As exposure is impossible to interpret as an indication of adverse effects caused by As since there is no reported "control background level" for these signs in the general Mexican population and hypo- and hyperpigmentation are cosmetic effects; and

6. The Tseng (1977) population is a sensitive subpopulation of humans. The reasons for such a conclusion are justified by the following facts. Inorganic As is detoxified by methylation in humans prior to urinary excretion (Hindmarsh and McCurdy, 1986; Marcus and Rispin, 1988) and animals fed diets deficient in nutrients such as methionine, choline, folic acid and/or vitamin $B_{12}$ have lower methylation rates due to decreased levels of S-adenosylmethionine, a necessary cofactor in transmethylation reactions (Shivapukar and Poirier, 1983). The Taiwanese population consumed inadequate amounts of protein (Irgolic, 1988) and would therefore be not expected to methylate As at the same rates as do humans with an adequate protein intake.

The enzymatic detoxification data suggest that there could be a "practical" threshold for As. This viewpoint is in accord with the preliminary Science Advisory Board report.

## VII. Summary.

The As workgroup has concluded that:

1. The Tseng report (1977) is the best available study to use for calculating a RfD,

2. The range of 4 to 9 ug As/liter of drinking water represents the best estimate of As concentrations in the drinking water in most of the 2,500 control group,

3. This 2,500 population is the appropriate group to use as the NOAEL group,

4. Based on the availible data, the rice and sweet potatoes would not make a major contribution to the overall daily As load. Accordingly, the workgroup believes that the RfD should be in the range of 0.4 to 0.8 ug/kg/day if an uncertainty factor is not used (See Table 3), and

5. No agreement on an UF could be reached by the members of the As Work Group.

In the Introduction, the As Work Group noted several areas in which more information and/or research were needed to remove the uncertainties mentioned in this report. Specifically, we see the need for detailed information on: the amounts of water ingested per day, an exposure distribution analysis of the study group to As, actual rice and sweet potato consumption, levels of inorganic/organic As in the rice and sweet potatoes with respect to As in the soil and whether possible contamination by As-containing pesticides could have occurred.

Table 1. Various Inorganic Arsenic Exposure Levels from Different Sources.

| | Drinking Water 4.5 l/day at | | | | Rice grown in . | | |
|---|---|---|---|---|---|---|---|
| | 1 ug/l | 4 ug/l | 9 ug/l | 17 ug/l | Natural Soil | As Soil | Li et al. Study (79) |
| ug As/day from Source | 5 | 18 | 41 | 77 | 2 | 4 | 16 |

Table 2. Various Daily Inorganic Arsenic Exposure Scenarios for Calculation of a NOAEL.

| As from Rice (ug/day) | Arsenic from Drinking Water (ug/day) | | | |
|---|---|---|---|---|
| | 5 | 18 | 41 | 77 |
| 2 | 7 | 20 | 43 | 79 |
| 4 | 9 | 24 | 45 | 81 |
| 16 | 21 | 34 | 57 | 93 |

Table 3. RfD Calculations from Various Exposures using ~~a~~ Uncertainty Factor

| | Total As from Water and Food (ug/day) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7 | 9 | 20 | 21 | 24 | 34 | 43 | 45 | 57 | 79 | 81 | 93 |
| RfD (ug/kg/day) (Total divided by 55 kg) | 0.1 | 0.2 | 0.4 | 0.4 | 0.4 | 0.6 | 0.8 | 0.8 | 1.0 | 1.4 | 1.5 | 1.7 |

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